APUA NEWSLETTER

2 0 0 0
VOLUME • EIGHTEEN
NUMBER • ONE

PUBLISHED . BY . THE . ALLIANCE . FOR . THE . PRUDEN˙ . USE . OF . ANTIBIOTICS

Antimicrobial Agents in Aquaculture: Potential Impact on Public Health

Frederick Angulo, Centers for Disease Control and Prevention, Foodborne and Diarrheal Diseases Branch, National Center for Infectious Diseases, Atlanta, Georgia, USA

Antimicrobial agents have been widely used in aquaculture to treat infections by a variety of bacterial pathogens of fish, including *Aeromonas hydrophila, Aeromonas salmonicida, Edwardsiella tarda, Pasteurella piscicida, Vibrio anguillarum,* and *Yersinia ruckeri.* Yet as this industry expands, questions arise concerning the consequences of this practice. Because these drugs are administered by mixing them with feed that is dispersed in the water, they directly dose the environment, resulting in selective pressures in the exposed ecosystem.[1] The emergence of antimicrobial resistance following use of antimicrobial agents in aquaculture has been identified both in bacteria that are fish pathogens and those that are not.[1]

A. salmonicida is an example of a fish pathogen which, in many countries, is frequently resistant to multiple drugs commonly used in aquaculture. These include sulfonamides, tetracycline, amoxicillin, trimethoprim-sulfadimethoxine and quinolones.[2,3] Often the first isolation of *A. salmonocida* resistant to a specific antimicrobial agent has been reported shortly after the introduction of the agent into aquaculture.[2] Similar correlations have been observed with other fish pathogens.[4]

Several studies have assessed the impact of antimicrobial agents used in aquaculture on nonpathogenic bacteria found in sediment and on fish farms. In one study, bacteria resistant to antimicrobial agents used on specific fish farms were isolated from sediment beneath the shellfish "netpens" on those farms.[5] In another study, resistant bacteria were isolated from the intestinal contents of natural and commercial fish species captured on fish farms. In contrast, no resistant bacteria were found in the intestinal contents of fish from untreated areas.[6]

Transfer of Resistance

Resistant bacteria that emerge as a result of antibiotic use in aquaculture can transfer their resistance to other bacteria. Many resistance determinants in fish pathogens are carried on transferable R plasmids.[7,8] Horizontal spread of plasmids from fish pathogens may therefore transfer resistance genes to other bacteria, including those that are pathogenic to humans.[8] This has been demonstrated in bacteria in the water of fish ponds[8] and in marine sediments.[9] Plasmids carrying resistance determinants have also been transferred in vitro from fish pathogens to human pathogens, such as *Vibrio cholerae,*[10] and *V. parahemolyticus,*[11] and to potential human pathogens, including *Escherichia coli.*[12] Furthermore, plasmids carrying multiple antimicrobial resistance determinants have been transferred in simulated natural microenvironments between bacterial pathogens of fish, humans, and other animals.[13] Transference of multidrug resistance occurred in Ecuador during the cholera epidemic that began in Latin America in 1991. Although the original epidemic strain of *V. cholerae* O1 was susceptible to the 12 antimicrobial agents tested, in coastal Ecuador it became multidrug resistant.[14] This epidemic began among persons working on shrimp farms, where multidrug resistance was present in non-cholera vibrios that were pathogenic to the shrimp. The resistance may have been transferred to *V. cholerae* O1 from other vibrios and may have conferred a selective advantage because of the local policy of chemoprophylaxis.[14]

Humans who are exposed to aquaculture settings may become infected with bacteria in several ways. For example, *Vibrio spp.*, part of the normal warm marine flora, can cause wound infections in persons with open cuts or abrasions exposed to seawater or marine life.[15] Bacteria from the aquaculture ecosystem may also be transmitted directly to humans through handling of fish. Recently, the fish pathogen *Streptococcus iniae* caused invasive infections in persons who handled store-bought aquacultured tilapia. The organism was isolated from the aquaculture ecosystem and on fish in grocery stores.[16] Similarly, a new biotype of *V. vulnificus* caused hundreds of serious infections among persons handling live tilapia produced by aquaculture in Israel.[17] Bacteria on fish may also be transmitted to humans when the aquacultured fish, or other foods that have been cross-contaminated, are eaten. *V. parahaemolyticus,* for example, is a common foodborne disease in Japan linked to the consumption of aquacultured fin fish.[18] Furthermore, *Salmonella*, a typical cause of foodborne disease, has been isolated from aquacultured fish and shrimp ponds.[19]

S. typhimurium DT104

Newly available molecular characterizations of antimicrobial resistance determinants provide further evidence of the transmission of resistance between aquaculture ecosystems and humans. Some of the antimicrobial resistance determinants in *Salmonella* serotype typhimurium definitive type 104 (DT104), for example, may have originated in aquaculture. *S. typhimurium* DT104, which is typically resistant to ampicillin, chloramphenicol, florofenicol, streptomycin, sulfonamides, and tetracycline, was first isolated from an ill person in 1985 and emerged during the 1990s as a leading cause of human *Salmonella* infections. Tetracycline resistance in *S. typhimurium* DT104 is due to a class G resistance gene.[20] The class G resistance determinant is rare and had not previously been reported from *Salmonella* isolates. It was first identified in 1981 in tetracycline-resistant isolates of *V. anguillarum*, a pathogen of fish.[21] Furthermore, the recently described novel florofenicol resistance gene *floR*, in *S. typhimurium* DT104, which also confers resistance to chloramphenicol, is almost identical by molecular sequence to the florofenicol resistance gene first described in *Photobacterium damsela*, another bacterium found in fish. Again, this resistance gene is rare and has not previously been found in *Salmonella* isolates.[22] Finally, all the antimicrobial resistance determinants in *S. typhimurium* DT104 are grouped on the chromosome within two distinct integrons and an intervening plasmid-derived sequence. The class G and *floR* determinants are located within the intervening plasmid-derived sequence. By molecular sequence, the plasmid-derived sequence is closely related (94% identity) to a plasmid identified in *Pasteurella piscicida*, a pathogen of fish.[20,23] These molecular characterizations strengthen the evidence that antimicrobial resistance determinants selected for in aquaculture ecosystems can be transmitted to bacteria that cause illness in humans, perhaps at a greater frequency than previously suggested.[24]

These data demonstrate that use of antimicrobial agents in aquaculture has selected for resistance among bacteria in the exposed ecosystems. This resistance can disseminate through the environment and can be transmitted to a variety of bacterial species, including bacteria that can infect humans.

References

1 World Health Organization. 1999. Joint FAO/NACA/WHO Study Group on food safety issues associated with products from aquaculture. WHO Technical Report Series, No. 883; Midtvedt T, Lingaas E. 1992. Putative public health risks of antibiotic resistance development in aquatic bacteria. In Chemotherapy in Aquaculture: from Theory to Reality, edited by C Michael, DJ Alderman. Paris, France: Office International de Epizooties, pp. 302-314.

2 Barnes AC, Hasting TS, Amyes GB. 1994. J Fish Diseases 17: 357-363; Inglis V, Millar SD, Richards RH. 1993. J Fish Diseases 16: 389-395; Tsoumas A, Alderman DJ, Rodgers J. 1989. J Fish Diseases 12: 493-507; Inglis V, Frerichs GN, Millar SD, et al. 1991. J Fish Diseases 14: 353-358.

3 Dalsgaard I, Nielsen B, Larsen JL. 1994. J Applied Bacteriology 77: 21-30.

4 DeGrandis SA, Stevenson MW. 1985. Antimicrobial Agents and Chemotherapy 27: 938-942; Takashima N, Aoki T, Kitao T. 1987. Fish pathology 20: 209-217.

5 Kerry J, Hiney M, Coyne R, et al. 1994. Aquaculture 123: 43-54.

6 Ervik A, Thorsen B, Eriksen V, et al. 1994. Diseases of Aquatic Organisms 18: 45-51.

7 Watanabe TT, Aoki Y, Ogata Y, et al. 1977. Annuals of the New York Academy of Science 182: 383-410; Aoki T. 1988. Microbiological Sciences 5: 219-223; Inglis V, Yimer E, Bacon EJ, et al. 1993. J Fish Diseases 16: 593-599.

8 Aoki T. Resistance plasmids and the risk of transfer. 1997. In Furunculosis: multidisciplinary fish disease research, edited by EM Bernoth. London, England: Academic Press, pp. 433-440.

9 Stewart GJ, Sinigalliano CD. 1990. Applied and Environmental Microbiology 56: 1818-1824.

10 Nakjima T, Suzuki M, Harada K, et al. 1983. Microbiology Immunology 27: 195-198.

11 Hayashi R, Harada K, Mitsuhashi S, et al. 1982. Microbiology and Immunology 26: 479-485.

12 Sandaa RA, Torsvik VL, Grokoyr J. 1992. Canadian J Micro 38: 1061-1065; Son R, Rusul G, Sahilah AM, et al. 1997. Letters of Applied Microbiology 24: 479-482.

13 Kruse H, Sorum H. 1994. Applied and Environmental Microbiology 60: 4015-4021.

14 Weber JT et al. 1994. Epidemiology and Infection 112: 1-11.

15 Blake PA, Merson MH, Weaver RE, et al. 1979. New England Journal of Medicine 300: 1-5.

16 Weinstein MR et al. 1997. New England Journal of Medicine 337: 589-594.

17 Bisharat N, Raz R. 1996. Lancet 348: 1585-1586.

18 Ministry of Health and Welfare. 1999. Infectious Agents Surveillance Report 20(7): 159-160.

19 Wyatt LE, Nickelson R, Vanderzant C. 1979. J Food Science 44: 1067-1069, 1073; Reilly PJ, Twiddy DR. 1992. Int J Food Microbiology 16: 293-301.

20 Briggs CE, Fratamico PM. 1999. Antimicrobial Agents and Chemotherapy 43: 846-849.

21 Zhao J, Aoki T. 1992. Microbiology and Immunology 36: 1051-1060.

22 Bolton LF, Kelley Lc, Lee MD, et al. 1999. Journal of Clinical Microbiology 37: 1348-1351.

23 Kim EH, Aoki T. 1993. Microbiology and Immunology 37: 103-109.

24 Smith P, Hiney MP, Samuelsen OB. 1994. Annual Review of Fish Diseases 4: 273-313.